Lymphoblastomas in Childhood

Cutaneous Manifestations

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• *The lymphoblastomas occurring in childhood are divided for purposes of discussion into lymphocytoma cutis, mycosis fungoides, lymphosarcoma, Hodgkin's disease, and leukemia. The cutaneous lesions may be either specific (as a result of the infiltration of the skin with specific cells of the conditions) or toxic (nonspecific). With the possible exception of mycosis fungoides, the cutaneous manifestations are not diagnostic. The final diagnosis depends upon microscopic examination of the specific tissue involved and the coordination of the clinical and microscopic findings.*

THE TERM *lymphoblastoma*, while open to certain legitimate criticism, has become fixed in medical literature and, to dermatologists at least, has a very definite meaning. While not all dermatologists agree as to just what conditions should be classed as lymphoblastomas,[1] most of them consider mycosis fungoides, leukemia, lymphosarcoma, and Hodgkin's disease to be the more important members of the group.[4, 52] Among the less important and even debatable members are lymphocytoma cutis and Spiegler-Fendt sarcoid. It is generally agreed that Spiegler-Fendt sarcoid should be classed as a lymphoblastoma.[17, 39] Spiegler's[63] patients with this disease died, as did Sweitzer's,[66] and one of Lewis's.[40] However, Fendt[21] did not give so bad a prognosis, and some of his patients either responded to therapy or had spontaneous resolution of the lesions. Bafverstedt[2] recently reclassified as lymphocytoma cutis many cases originally considered to be Spiegler-Fendt sarcoid. Lewis,[41] in discussing the paper of Loveman and Fliegelman,[43] stated that "from the evidence given by the authors, it would seem that the disease under discussion is identical with the localized form of Spiegler-Fendt sarcoid." While some observers feel that lymphocytoma cutis is always benign,[17, 43, 49] others do not share that view,[41, 48, 65a] and all agree that prolonged and careful observation is necessary to make sure there is not malignant change. Even though the question of the exact relationship of these two conditions to each other and to the other lymphoblastomas has not been settled, the author looks upon lymphocytoma cutis as a relatively benign lymphoblastoma. The condition must be considered in the differential diagnosis of the lymphoblastomas, and while it apparently remains benign in most cases, it may become malignant. In the present discussion Spiegler-Fendt sarcoid and giant follicular lymphoma will be placed in the lymphosarcoma category.[17, 31, 54, 64]

Since, to the best of the author's knowledge, no report of reticulum cell sarcoma in childhood (other than in bone[31]) has appeared in the literature, any discussion of its place in the classification will be omitted.

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Of the leukemias, the acute form is the most common in children. Chronic myeloid leukemia is uncommon, and chronic lymphatic leukemia does not occur.[12, 13]

Lymphocytoma cutis, mycosis fungoides, lymphosarcoma (including Spiegler-Fendt sarcoid and giant follicular lymphoma), Hodgkin's disease and leukemia have been reported in preadolescent children. Because the statistics on the lymphoblastomas are for the most part given in relation to decades of life, lymphoblastoma occurring in the first two decades (rather than before puberty only) will be considered in this presentation.

Lymphocytoma cutis (benign lymphadenoid granuloma of the skin, miliary lymphocytoma, lymphadenosis benigna cutis) is rare in childhood. The youngest patient of record, a four-year-old child observed by Kaufman-Wolf,[32] had lesions on the scrotum. Localized lesions are the form usually seen in children.[2] Loveman and Fliegelman[43] and Mopper and Rogin[49] have reviewed the literature and have reported cases in adults. The clinical appearance varies considerably, and the lesions may resemble epithelioma adenoides cysticum, rhinophyma, moles or basal cell epithelioma. Rarely if ever do the lesions ulcerate. Becker[5] stated that when pressure is applied to a glass slide on the skin, an apple jelly color persists, as in lupus vulgaris. Long observation and repeated studies of the blood and bone marrow are necessary to rule out malignant lymphoblastoma.

Mycosis fungoides (granuloma fungoides) is es-

sentially a disease of adults, although occasionally it occurs during the first two decades of life.[29, 42, 52, 56, 59] Apparently the youngest patient was a three-year-old boy reported upon by Hathaway.[29] He had a single lesion on the face, which responded to x-ray therapy. Ormsby and Montgomery[52] cited a report of mycosis fungoides in a child six years of age.

There is nothing in the literature leading the author to believe that mycosis fungoides in children differs in any way from that in adults. Mycosis fungoides usually begins as plaques of a rather nondescript scaling, pruritic dermatitis (the premycotic stage). The plaques become infiltrated, and tumors, which eventually ulcerate, develop. The condition spreads, and ultimately causes death. Although mycosis fungoides may remain localized to the skin throughout its course, not infrequently it becomes a generalized systemic disease with features like those of leukemia or one of the other types of lymphoblastoma.[36, 38, 46, 47, 52, 73] In the premycotic stage, diagnosis may be difficult or impossible. By the time infiltration and tumors appear, the syndrome is quite characteristic. Pruritus may be severe in all stages of mycosis fungoides. Occasionally pruritus alone is the initial symptom. Mycosis fungoides may also begin as poikiloderma atrophicans vasculare or as a poikiloderma-like eruption.[51, 69] It may resemble psoriasis, or it may begin as tumors with ulceration (the d'emblee type). Occasionally it begins as erythrodermia.[46, 59]

Leukemia, Hodgkin's disease, and lymphosarcoma have many cutaneous symptoms in common and for the purposes of this presentation can be considered together. First, however, it might be well to discuss the two special varieties of lymphosarcoma, Spiegler-Fendt sarcoid and follicular lymphoblastoma (follicular lymphoma, follicular type of malignant lymphoma, giant follicular lymphadenopathy, giant lymph follicular hyperplasia of lymph nodes and spleen, Brill-Symmer's disease), because each of them has a cutaneous picture quite different from that seen in typical lymphosarcoma. Both conditions are rare in childhood.

Spiegler-Fendt sarcoid appears in either a localized or disseminated form. Both forms occur in children.[40] The cutaneous manifestations of the localized form are apparently identical with those described under lymphocytoma cutis. In the disseminated form, generalized cutaneous or subcutaneous nodules, up to 2.5 or 3.0 cm. in diameter, develop. Plaques sometimes appear. The color of the skin varies from normal to deep crimson or deep red. The nodules grow to a certain size and then are static. Spontaneous regression occasionally occurs.

Follicular lymphoblastoma has been thoroughly reviewed by Gall and co-workers[24] and Combes and Bluefarb.[10] Gall, in a review of 69 cases, noted that in 3.5 per cent of them the onset was before the patient was 20 years of age. Eighty-nine per cent of the patients had peripheral lymph nodes, and 5 per cent of them had cutaneous involvement which consisted of "a few isolated, raised, firm, brownish to reddish nodules." It was reported that no diffused lesions were observed. Herpes zoster occurred in three cases. Combes and Bluefarb reviewed reports of 72 cases in the literature, and reported on 15 patients they had observed, 14 of them males. The youngest patient in the series of 87 cases reviewed was 15 years of age, the eldest 80. In the 15 cases Combes and Bluefarb had observed, the skin conditions resembled those of allergic eczema (including exfoliative dermatitis), chronic discoid and lichenoid dermatitis, and a third condition that was clinically diagnosed as mycosis fungoides. One patient, aged 17, had dermatitis resembling chronic discoid and lichenoid dermatitis, associated with giant follicular lymphadenopathy of two years' duration. Microscopic examination of the skin was carried out and the disease could be classified only as "chronic dermatitis."

The cutaneous symptoms of typical leukemia, Hodgkin's disease and lymphosarcoma are usually divided into the toxic or nonspecific lesions, and specific lesions—those containing true tumor cells. This division is not absolute, for so-called toxic lesions may contain tumor cells.[25, 39] In addition toxic lesions may later be the site of development of specific lesions, and sometimes tumor cells may be present in skin which, to clinical observation, seems normal.[22, 35] Specific lesions may develop at the sites of skin lesions in no way related to the lymphoblastoma (varicella,[22] trauma[35]). The nonspecific lesions are in no way characteristic, but may be suggestive of the underlying condition. Almost every type of lesion the skin is capable of producing may occur. Pruritus, either with or without skin lesions, is common. Pigmentation, macules, papules, lichenification and exfoliative dermatitis may occur,[25] and also bullous lesions,[17, 60] pustules, and vesicles.[75] Alopecia, atrophy, dryness and hyperkeratosis have been reported. Icterus, urticaria and bouts of unexplained hyperhidrosis may develop.[9] Herpes zoster may complicate almost any of the lymphoblastomas.[8, 72]

Especially in leukemia, hemorrhage in the skin and mucous membrane, stomatitis, noma, pallor and enlargement of the abdomen are not infrequent.[18] Some symptoms, such as dyspnea, cough, intestinal obstruction, abdominal pain, nausea, vomiting and diarrhea, may be owing to the clinical location of

the tumor mass, and are not characteristic of lymphoblastoma.[11, 15, 44, 53] Anemia and fever occur some time during the course of the disease in most patients. The so-called Pel-Ebstein fever is said to be quite characteristic of Hodgkin's disease, but may occur in other conditions also.

The cytologic structure in nonspecific cutaneous lesions is, of course, not characteristic and unless by good fortune specific cells are observed in the section, histologic examination can be of little help. However, as the underlying condition is usually pronounced, histologic identification may not be necessary for diagnosis.

Specific cutaneous lesions may consist of generalized exfoliative dermatitis (which may also occur as a nonspecific symptom), cutaneous or subcutaneous nodules, as well as tumors and plaques, and enlarged lymph nodes. Ulceration occasionally occurs, particularly in Hodgkin's disease.[60, 67, 73]

A special word should be said about chloroma, which is a manifestation of acute leukemia.[17] Over 50 per cent of the patients with these greenish tumors are under 20 years of age. The tumors may be cutaneous or may be located in positions to cause symptoms owing to pressure on adjacent organs.

The final diagnosis in any of these conditions depends upon the examination of specific tissue, be it skin, lymph node, bone marrow or blood, and the coordination of the clinical and microscopic observations.

Prognosis. The course of all the lymphoblastomas seems to be somewhat more rapid in children than it is in adults.[14, 62] However, there is great variation from case to case. Leukemia, in particular, usually runs an acute fulminating course. Follicular lymphoma and Spiegler-Fendt sarcoid progress much less swiftly than does typical lymphosarcoma. Lymphocytoma is usually benign.

Treatment. Lymphocytoma is very radiosensitive and, while it responds to radiation therapy, recurrence is the rule.[43, 49] It is also said to respond to arsenic. Excision may be curative.[65b] Occasional spontaneous remission occurs in this condition, as it does at times in other types of the lymphoblastomas.

Bierman[6] has given a very complete review of the treatment of the other lymphoblastomas. Follicular lymphomas frequently respond to x-ray therapy or to surgical excision. Single focus lymphomas may be removed surgically, and that treatment followed with intensive x-ray therapy (until further evaluation proves the latter to be of no additional value). In acute leukemia of childhood, radiation therapy, urethane and nitrogen mustard are of little or no value.[54] The most satisfactory treatment seems to be administration of the folic acid antagonists.[16, 19, 20, 30, 54, 70] Leukemia in adults does not respond to folic acid antagonists as well as does the disease in children.[16, 19, 30] Toxic symptoms are common, and at best the treatment is only palliative. Radioactive substances are still in the experimental stage. Nitrogen mustard is palliative in Hodgkin's disease, lymphosarcoma and mycosis fungoides. It is also somewhat effective in giant follicular lymphoma. Its use is frequently complicated by granulopenia. Triethylene melamine has about the same action as does nitrogen mustard.[61] Colchicine has resulted in temporary improvement in some cases of mycosis fungoides.[68] (The author has under observation a man believed to have mycosis fungoides. He had relief of pruritus for four months from colchicine by mouth. It was then no longer effective.) ACTH and cortisone are temporarily helpful in some cases of lymphoblastoma. Some patients are made worse.[37, 55, 57]

DISCUSSION

It should be stressed that the clinical manifestations of these conditions, with the possible exception of mycosis fungoides, are not specific or diagnostic. The classification of a patient with lymphoblastoma, or even the diagnosis of lymphoblastoma, may be difficult and require prolonged observation.[9, 36, 46, 64] The difficulty is well illustrated by the case of a patient who was presented before a meeting of the Los Angeles Dermatological Society.[50]

The patient, a 9-year-old white boy, was first observed by the author March 17, 1951, because of a lesion "like a little boil" which had appeared on the left side of the nose two or three weeks previously. No pus was expressed from the lesion and no similar lesion had ever been present before. There was no history of injury preceding onset. Upon examination the lesion was observed to be a semi-hard erythematous nodule 1.2 cm. in diameter. The submaxillary nodes were not enlarged. The left anterior cervical lymph nodes were possibly enlarged, as was one in the left axilla. No abnormalities were noted upon examination of bone marrow. Results of examination of the blood and the urine were within normal limits. Only chronic inflammation was noted in microscopic examination of a left cervical lymph node that was removed April 2, 1951. The lesion was excised in toto April 12, 1951. A year later there was no evidence of recurrence.

It was generally agreed by those attending the presentation of the patient that the lesion was lymphoblastoma of some type. Winer[74] favored a diagnosis of reticulum cell sarcoma. Subsequently, the sections were studied by other dermatopathologists and pathologists, with the following diagnoses: Cutaneous lymphoblastoma, possible cutaneous reticuloendotheliosis, possible Letterer-Siwe disease, and probable cutaneous lymphoma.

Diagnosis and classification of these conditions are not helped by the fact that some patients show

characteristics of more than one of the lymphoblastomas. Keim[34] reported a case (Case 10) in which there was evidence of mycosis fungoides and lymphatic leukemia. In a case reported by Miller[45] (Case 4) the pathologic changes of Hodgkin's disease were noted in 14 lymph nodes, whereas in one node the structure was characteristic of small cell lymphosarcoma. Ginsburg[26, 27] found little biologic difference between lymphosarcoma and Hodgkin's disease, and pointed out that there is no clinical way of differentiating them. The histologic structure is not always diagnostic. Perhaps lymph node imprints[67] will help in differentiation. The observation that some lymphoblastomas apparently change from one type to another, and that transition forms exist between all the groups,[4, 23, 38, 39, 70, 73] does not help to clarify the situation.

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Film Library Has Record Year

RALPH P. CREER, secretary of the A.M.A. Committee on Medical Motion Pictures, reports that 2,088 medical motion pictures were lent to medical societies, medical schools, hospitals and other scientific groups during 1952. This represents an increase of 516 over 1951, and is the greatest number of films distributed since the A.M.A. motion picture library was started.

—A.M.A. *Secretary's Letter*